A compact guide to the systematic review and meta-analysis of the literature in neuroscience

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Response to Reviewers Comments:

Reviewer: A

General Comment: I read this paper as a neuroscientist who might be part of the target audience. My impression is that it presents a very simplified (compact) overview for how to conduct a systematic review and meta-analysis (SRMAN). I very briefly reviewed the two papers that it is based on (Vesterinen et al. 2014 and Muka et al. 2020) and it does seem to follow and synthesize the process outlined in those papers, but in an extremely simplified form. It could therefore be useful a starting point for a researcher interested in conducting SRMAN but I suspect its main utility is in pointing the reader towards more comprehensive resources.

#General Response: Thanks for all your comments. We tried to incorporate all your suggestions in our new version of the manuscript.

Major concerns and questions

1. I wonder if this paper really does enough that is distinct from Vesterinen et al. (2014) to warrant neuroscientists starting here, rather than referring directly to Vesterinen (for animals) or maybe Muka (for humans). To me, the advice contained in this guide all seemed quite general and applicable to virtually any field. I think there needs to be some additional clarity as well about whether this for neuroscience generally or for animal studies only (implied by references to "basic neuroscience" but I don't think this automatically means animal-only).

Response: Thanks for your comments. We have restructured the entire manuscript intending to clarify these issues. We added references and examples applicable to neurosciences in the protocol elaboration phase. For example, see the item "*Screening or selection strategy*"; "See examples of protocols presenting screening strategies in the field of neuroscience by Hohls (37), Ramos-Hryb (33) and Bolzan and Lino de Oliveira (34)".

2. Thinking about my own field within neuroscience, much of the work is exploratory and not closely replicated. A particular mechanism is rarely manipulated the same way for the same outcome measure. How much can or should we collapse things together conceptually? For example, is it OK to meta-analyze across similar but distinct outcomes (e.g. 4 different measures of stress)? What about if the mechanism is close (e.g. the same drug or drug-class, but injected into different brain regions) while the outcome measure is the same?

Response: Thank you for your comment. It is typical for studies in this area to show results similar to what you could do. In this case, one possibility to investigate an effect size in heterogeneous ones is to stratify in subgroup analyses. We mentioned this in the item "*Meta-analysis"*.

3. A few times within the paper, references are made to collaborations with librarians or statisticians. I felt like this was a little vague. For example, can a librarian really help me with elaboration of a research question? Or should I really be seeking their advice more specifically for assistance with scholarly databases and reference management software?

Response: Thank you for your comment. In our experience librarians provided good instruction how to prepare a searchable question using mnemonic tools (like PICO) and use bibliographic databases and reference management (we added a remark about it in the topic "*Search strategy"* in the section: Phase 2).

4. Many acronyms are described (PICO, ECLIPSE, SPICE, SPIDER), but it seems only in passing. What are the relative advantages and disadvantages of these approaches? For example, is, say, SPIDER, better for someone trying to do an SRMAN on human EEG data? Or how suitable would ECLIPSE be for neurobiological results from animal studies?

Response: Thank you for your comment. The mentioned the use of ECLIPSE, SPICE, SPIDER approaches, besides PICO and variations, to provide flexible alternatives to the reader. We agree that the information was left vague when its advantages and disadvantages. These can be useful when specific types of research (e.g., *in vitro*, *in vivo*, *ex vivo*, or brain imaging) are the main interest of the review. Therefore, we have added this information.

5. I found the structure of the article a little confusing. The main description of each phase was quite brief, but the "Brief description of steps encompassing the five phases of SRMAN" was, in contrast, quite long. Maybe a restructuring of the paper is in order so that more detail is provided in the main text and brief descriptions or summaries are presented in another way (e.g. text box or summary table).
Response: Thanks for your comment and suggestions. We have restructured the text completely by adding more details in the phase 2 (elaboration of a review protocol). Also, we've added 3 tables:
Table 1, for the PICO tool: categories, definitions and examples.
Table 2, for the description of a generic search strategy elaborated to obtain relevant publications to answer a hypothetical review question created using the PICO tool.
Table 3, for the description of generic inclusion and exclusion criteria to a screening strategy of studies relevant to answer a hypothetical review question created using PICO tool.

Minor concerns and questions
1. One thing I appreciated in Vesterinen is how they noted which software packages were proprietary. I recommend that the authors highlight, in particular, which software packages are free (and open source) to help the budget-constrained neuroscientist more quickly identify the best approach.
Response: Thanks for your suggestion. We make suggestions of selected free resources to implement each step of an SRMAN in any field of nonclinical research, including neurosciences. We have added this information in the section: Phase 4 (protocol implementation).

2. In Phase 3 it is suggested that PROSPERO is the "most important public platform accepting registrations for rapid reviews, umbrella reviews, and systematic reviews..." Why is this? Is it because of the preregistration templates or because this is the most frequently cited location for preregistered SRMANs (and related review types)? Can other platforms, like Open Science Framework (osf.io) be used just as well?
Response: Thanks for your comment. We cite PROSPERO as the most important platform for review registration because it is a large international database of systematic reviews used for registries in different areas: health, social care, welfare, public health, education, crime, justice, international development and others. In other words, PROSPERO concentrates most of the records of systematic reviews, but the Open Science Framework (OSF) can also be used. We have added this information in the last paragraph of section: phase 3 (protocol preregistration).

3. I think the paper might benefit from sketching out an example situation. This would help me to better understand exactly what each of the phases involves and how it might look in my own neuroscience research.
Response: We agree with your comment and have added some examples to the neuroscience-focused handwritten text. For example, definitions for population, intervention, control, and outcomes commonly used in this area, practical examples of protocols, and others. In addition to rearranging the text, we have provided a figure (Figure 1) with an illustration of all the steps. We hope you agree with what you thought.

Reviewer: B
I am sympathetic to the need for clear guidelines and how-to manuals for systematic reviews and meta-analyses. I don't see anything incorrect in the present manuscript; however, I don't understand the goal of the manuscript. The authors present multiple tools that can be used for SRs and MAs and described what an SR/MA consists of. There is very little in the manuscript specific to neuroscience. The title says the manuscript is a "guide" and the abstract states "These methods involve individually simple decisions, which may become complex when considering the whole process.". In its current form, I feel the manuscript is poorly written as a guide and that it makes SR/MAs seem very complex because the authors describe all the information in the main text and don't organize information into tables, steps, diagrams, or resources (beyond the 5 overarching steps they describe). I feel the manuscript could be published with minor edits, but has limited value. Reorganizing the information into amore "guide" format that has step-by-step instructions and is specific to basic neuroscience might be more useful. However, there may already be more established and thorough guidelines that exist (e.g., Cochrane, Johanna-Briggs Institute, PRISMA, or others). I would recommend systematically searching what guidelines already exist and then organizing this manuscript so that it adds value beyond what already exists (or if this has already been done, explaining more clearly what value this manuscript adds). Although, I leave it to the editors and authors to decide how to move forward.
Response: Thanks for your comments. We agree with your comments and have restructured the entire text of this manuscript. We hope it's better and clearer now. We better detail the phase involved in the process

of elaborating the research question, elaborating the protocol, preregistration, implementing or executing and disseminating the data. We added tables for the PICO tool: categories, definitions and examples; for the description of a generic search strategy elaborated to obtain relevant publications to answer a hypothetical review question created using the PICO tool; and, for the description of generic inclusion and exclusion criteria to a screening strategy of studies relevant to answer a hypothetical review question created using PICO tool. We agree and find your suggestions helpful on reorganizing the information and highlighting the purpose of this manuscript for the field of neuroscience. For this, we add examples of protocols published in this area that can serve as examples for some steps in the preparation and execution of a systematic review and meta-analysis.